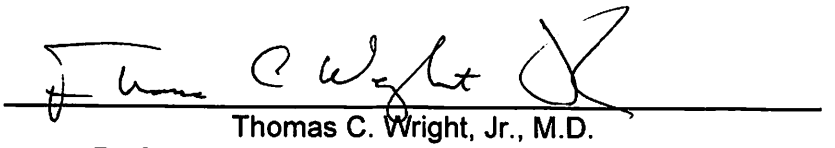
EXHIBIT B

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC. PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL No. 2327**
THIS DOCUMENT RELATES TO WAVE I	**JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

EXPERT REPORT OF THOMAS C. WRIGHT JR., M.D.

Prepared by



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Background and Qualifications

I, Thomas C Wright, Jr. MD, am a board certified Anatomic Pathologist with 28 years of experience in gynecological, obstetrical, and cytological pathology. From 1989 - 2011 I was an attending pathologist in Division of Gynecological, Obstetrical, and Cytological Pathology at Columbia University, New York, NY and from 1998-2011 I was the Director of the Division of Gynecological, Obstetrical, and Cytological Pathology at Columbia University. I am currently a Professor Emeritus of Pathology and Cell Biology at Columbia University and work as a gynecological and cytological pathologist at Enzo Clinical Laboratories, in Farmingdale, NY. I actively participate as a gynecological pathologist for multiple research studies and clinical trials. During my work as a gynecological pathologist I evaluate explanted mesh material from the vagina.

In addition to my extensive experience in gynecologic pathology, I also have specific experience evaluating host tissue responses to implanted materials in the female gynecologic tract. From 1997 to 2008 I served as the expert gynecologic pathologist for Conceptus. In that role, I evaluated the host tissue response to a variety of different biocompatible materials. I then served as the study pathologist for the company's pivotal FDA trial, as well as subsequent post-approval study. During the course of this work I evaluated and quantified host tissue responses and ingrowth of fibrosis in implanted intra-fallopian devices.

Reason for Using Implanted Polypropylene Mesh to Strengthen Vaginal Tissues in Women with Pelvic Organ Prolapse

Pelvic organ prolapse (POP) is reported to affect one in three women and each year in the U.S. 200,000 women undergo surgical correction of pelvic organ prolapse.[1,2] Traditional surgical correction of POP has a relatively high failure rate. Up to 70% of women who undergo traditional surgical repair for pelvic organ prolapse are reported to have recurrent prolapse and 29% of surgically managed women require reoperation.[3,4] Part of the reason for the high rate of recurrent prolapse after surgical correction is that like abdominal hernia patients, POP prolapse patients have weakened connective tissue which is more susceptible to forming architectural defects. Hernia patients have been found to have a different fibroblast phenotype than do non-hernia patients and these altered fibroblasts produce collagen that is both quantitatively and qualitatively abnormal. In most patients collagen consists primarily of Type I and Type III

collagen fibrils that are produced in a 4:1 ratio. Hernia patients over express Type III collagen type.[5,6] The excess in Type III collagen inhibits cross-linking of Type I collagen and cross-linking between Type I and Type III collagen. This results in collagen fibers that are inherently thinner and weaker and which undergo lysis more readily. Similar alterations in Type I to Type III collagen ratios have been found in women with POP.[7] In addition to collagen alterations of women with POP, the amount of smooth muscle actin (SMA) in the muscularis of the vaginal wall is reduced.[8] The finding of alterations in the connective tissue of the vaginal wall in women with POP suggests that an inherent laxity or weakness of the connective tissue contributes to POP. Therefore synthetic mesh materials were introduced to reinforce weakened native tissues during pelvic reconstructive surgery in women with pelvic prolapse of the bladder or rectum in order to improve clinical outcomes and reduce surgical failure rates.[3] Synthetic mesh implants have been shown to be stronger and more resistant than biological tissue.[9,10] A number of randomized controlled trials comparing outcomes after mesh repair surgery versus traditional surgery and many of these have shown that mesh-based repairs have higher success rates than traditional surgery.[11-13]

Inflammatory Response and Foreign Body Response to Foreign Materials

Although the host inflammatory and foreign body response to implanted synthetic foreign material follows a fairly typical sequence of events, the specifics of the response may vary considerably depending on the composition of the foreign material.[14] In addition, the host response will vary somewhat depending on the site and the species in which a synthetic foreign material is implanted. Nevertheless, in general, host inflammatory and foreign body responses are comparable between sites and the typical species utilized for biocompatibility and tissue response studies.

Acute Phase of the Response

Implanted foreign material very quickly get covered by a layer consisting of adsorbed host proteins. This process follows a fixed hierarchical pattern that is termed the *Vroman effect* after the person who described it. Initially, low molecular weight proteins like albumin that have the highest mobility are adsorbed to the foreign material. Subsequently, complex higher molecular weight, and therefore less mobile, proteins such as fibrinogen, immunoglobulins, and

extracellular matrix molecules are also adsorbed. For foreign materials implanted in sites without mechanical turbulence, the initial protein deposition typically takes the following sequence: albumin, globulin, fibrinogen, fibronectin, factor seven, and high molecular weight kininogen.[15] Subsequently, the adsorbed proteins undergo conformational changes that renders them immunogenic. The immunogenic biofilm then leads to complement activation, fibrin clot formation, and the binding of antibodies to the foreign material. These processes elicit an initial acute inflammatory response consisting primarily of leukocytes. These are initially polymorpholeukocytes (PMN) but the PMN are later joined by monocytes that become activated. Activated monocytes differentiate into tissue macrophages that play a key role in the subsequent overall host response. Tissue macrophages and other cells responding to the foreign material produce many different cytokines that promote the directional migration of other leukocytes to the site of the foreign material. Macrophages also produce factors that stimulate the migration and proliferation of fibroblasts and blood vessels, the synthesis of collagen, and enzymes that remodel connective tissues. Therefore, during the acute inflammatory phase of the tissue response to an implanted foreign material, there are a large number of PMNs, monocytes, macrophages, as well as a considerable number of small proliferating blood vessels and proliferating fibroblasts. During the acute phase of response there is minimal dense fibrosis.

Chronic Healing Phase of the Response

With time, the host response to the implanted foreign material changes from the acute inflammatory phase to the chronic healing phase. In this context the term chronic is not meant to denote a troubling condition. Instead the term chronic in this context indicates that cellular and collagen composition surrounding the implanted foreign material changes from what is initially present during the acute phase of the host response. During the chronic healing phase the number of inflammatory cells decreases as do the number of small capillaries. The type and numbers of the inflammatory cells change from predominantly PMN and monocytes to many more macrophages, as well as lymphocytes, plasma cells, and some eosinophils. During this period foreign body giant cells also develop. Foreign body giant cells are simply activated macrophages that have developed large amounts of cytoplasm and become multinucleated. These foreign body giant cells are typically observed around foreign materials, including those that are biocompatible, when the foreign materials are too large for phagocytosis and also do not elicit a specific inflammatory or immune response. Frequently the foreign body giant cells are immediately apposed to the surface of the foreign material. During the chronic healing

phase fibroblasts become more prominent and they begin to deposit more collagen and extracellular matrix proteins.

Factors Influencing the Host Response to Implanted Synthetic Mesh

In order to form a robust, long-lasting repair of a defect in the abdominal wall (i.e., hernia surgery) or the vaginal wall (i.e., POP surgery), the implanted synthetic mesh needs to become fully integrated into the tissue at the site of repair. Although all of the current synthetic mesh materials utilized in surgery are considered biocompatible, the different physical and structural properties of the synthetic materials influence their integration. Synthetic meshes can be made from knitted, single-fiber filaments (monofilament materials) or they can be made of braided multifilament fibers. These are then woven in different ways and with different pore sizes. Moreover, the resulting meshes have different physical properties such as stiffness and breaking strength. In 1997, Amid evaluated the importance of specific physical properties on synthetic meshes utilized for hernia surgery.[16] The most important properties that he identified were porosity and the pore size. Based on pore size he identified four basic types.

Type I; totally macro porous meshes such as Prolene. These meshes have pores larger than 75 um that he hypothesized is a required pore size for admission of macrophages, fibroblasts, blood vessels, and collagen fibers into the pores.

Type II; totally microporous mesh that contain pores that are less than 10 um in at least one of their three dimensions

Type III; macroporous mesh with multifilamentous or microporous components - this includes braided PP mesh

Type IV; submicronic pore size

As stated at the beginning of this section, in order to form a robust, long-lasting repair and support the weakened tissues, a mesh needs to become fully incorporated into the adjacent host tissue. It is generally accepted that the pore size of the mesh should be at least 75 um to facilitate the entry of macrophages, blood vessels and fibroblasts. Meshes with pore sizes less than 75 um tend to undergo scar encapsulation. When scar encapsulation occurs dense fibrous tissue forms around the mesh as a whole, but the fibrous tissue does not actually incorporate individual fibers. Peak ingrowth occurs with meshes that have pores of 400-500 um in diameter. It is generally accepted that monofilament meshes are preferred because multifilament (braided) meshes, Amid Type III meshes, have spaces within the multifilament individual fibers that are

less than 10 um in diameter. Such small spaces are not readily accessible to leukocytes, macrophages, and fibroblasts (that are typically 10-20 um).

Histologic Studies of the Integration of Implanted Polypropylene (PP) Mesh into the Host Tissue

Animal studies at non-genital sites

Animal studies have examined the host response to variety of types of implanted synthetic mesh material. In 1995, Bellon *et al*. evaluated host tissue response to polypropylene (PP) mesh (*Marlex*) implanted in the abdominal wall of New Zealand white rabbits.[17] 14 days after implantation the polypropylene mesh was surrounded on both its internal and external sides by loose scar tissue. The scar tissue infiltrated the mesh material and did not encapsulate it. Individual mesh fibers were enveloped by one to two cell layers and there were large numbers of macrophages present. Numerous blood vessels were distributed within the interstices of the mesh. After 30 days, the loose connective tissue was confined to spaces between the filaments. There was a dense fibrous tissue at the mesh-visceral peritoneum interface. Overall, at 30 days there were fewer macrophages than seen at day 14. However the number of cells accumulating around the mesh fibers had increased. Between 14 and 30 days the number of blood vessels continued to increase. At 90 days the healing process appeared to have stabilized. The number of macrophages was reduced, however the number of foreign body giant cells continued to increase and a number of large granulomas appeared around the microfilaments of the mesh. The number of blood vessels had continued to increase and by day 90 there was a large vascular component. It should be noted that macroscopically there was good tolerance to the implanted PP mesh.

Hutchinson *et al.* conducted a subcutaneous implantation study in Long-Evans rats to assess the host response and qualitative integration of PP-based meshes.[18] The implanted meshes were placed in pockets that were surgically made between the skin and the underlying connective tissue and sutured shut. Rats were sacrificed at 7, 28, 63, and 91 days post-implantation. Four different types of PP-based meshes were used: *Prolene soft*, *VYPRO*-62* that is an early prototype of a composite mesh containing absorbable polyglactin 910 filaments, *Bard* mesh that is a commonly used monofilament mesh, and *Surgipro* that has a multifilament construction. Inflammation and assessment of integration (fibrosis) at the different time points was assessed using a 0-4 scale.

	Bard mesh		**Surgipro**		**Prolene soft**	
	Inflammation	*Fibrosis*	*Inflammation*	*Fibrosis*	*Inflammation*	*Fibrosis*
7 days	mild chronic	mild	minimal-mild FBGCR	minimal-mild	minimal-mild chronic	mild
Later (*28, 63, 91 days*)	minimal-mild chronic	minimal-mild	mild FBGCR	minimal-mild	mild	minimal-mild

Overall, the inflammatory reaction to the four different PP-based meshes of different construction was relatively similar and all were considered "biocompatible". All had sufficient porosity to allow ingrowth of connective tissue.

Boulanger *et al.* conducted another animal study to evaluate tissue integration and tolerance to five different meshes used in genital prolapse surgery.[19] In this study the meshes were placed on the peritoneum of pigs for 10 weeks. 10 weeks was selected based on the studies of Bellon *et al.* and others because it is close to the equilibrium state of healing and incorporation in previous studies. Non-absorbable polypropylene (PP) meshes (*Prolene* and *Prolene Soft*) induced less inflammation than did a non-absorbable polyethylene terephthalate mesh (*Mersuture*) or the semi-absorbable mesh made of Polyglactin 910 and polypropylene (*Vypro*). The *Prolene* and *Prolene Soft* meshes induced weak lymphocyte and macrophage reactions. Both *Prolene* and *Prolene Soft* were well integrated into the surrounding tissue with a "rich" fibrous connective tissue and "rich" vascularization. Collagen encompassed bunches of polypropylene fibers and penetrated deeply between them. In comparison, the tissue integration of *Mersuture* was not as good. The authors concluded that monofilament macroporous meshes (Amid Type I meshes) made out of PP seemed to be the best integrated and tolerated.

Animal studies at genital sites

Additional work has evaluated the host response to synthetic mesh materials implanted at genital sites in animal models.[20] The model that has been best studied is implantation of surgical mesh into the rabbit vagina.

Hilger *et al.* utilized a New Zealand white rabbit model to evaluate four different graft materials, one of which was porcine collagen-coated PP mesh (*Pelvicsoft*), that were implanted in the abdominal and vaginal walls.[21] Although size of the study was small (n=20), this was one

of the first studies to compare host response to graft materials implanted in the abdominal and vaginal walls. Grafts were harvested at 6 and 12 weeks and evaluated both histologically and biomechanically. The histological appearance of all four graft materials including the porcine collagen coated PP mesh was similar at both time periods (6 and 12 weeks) and also similar for the grafts implanted at the two sites. Histologically, the porcine collagen-coated PP mesh showed minimal inflammatory response and minimal neovascularization. There was moderate collagen ingrowth into the mesh and a foreign body giant cell reaction, irrespective of whether mesh was implanted in the abdominal or vaginal wall.

Subsequently, Huffaker *et al.* used this same rabbit model to compare the host response to vaginally implanted porcine collagen-coated monofilament PP mesh (*Pelvitex*) and uncoated monofilament PP mesh (*Gynemesh PS*, Ethicon).[22] After 12 weeks of implantation both materials had elicited a mild chronic inflammatory response with minimal fibrosis. There was good host tissue incorporation within the grafts. Inflammatory cells consisted of multinucleated foreign body giant cells, macrophages, lymphocytes, and plasma cells with few PMN. They also measured cellular proliferation using Ki-67 immunostaining and apoptosis (cell death) using the TUNEL assay. At 12 weeks there was a low rate of cell proliferation (<1% Ki-67 labeled cells) in the host tissues surrounding both types of PP mesh. There also was a low rate of apoptotic cells in tissues surrounding the PP mesh (<1% TUNEL labeled cells). These findings indicate that the initial, acute reaction associated with mesh insertion is resolved at 12 weeks.

Subsequently a larger, longer duration, study compared the host response to grafts implanted in the abdominal and vaginal walls in the New Zealand white rabbit model. Two types of graft material were evaluated, monofilament PP mesh (*Gynemesh PS*, Ethicon) and crosslinked, perforated, acellular PS collagen (PelvicSoft Acellular Collagen Biomesh). In this study the grafts were left in the rabbits for 9 months. Overall, the PP mesh elicited a milder and more uniform chronic inflammatory response than did the acellular PS collagen. At both sites (*i.e.*, vaginal and abdominal) there was good host tissue incorporation into the PP mesh. It is important to stress that the host response to PP mesh in this study at 9 months was similar to what this same group had documented in the previous study at 12 weeks. The host tissue incorporated into the vaginally implanted PP mesh consisted of blood vessels, fibroblasts, new collagen, and some smooth muscle. Inflammatory cells seen at the PP mesh implantation site at 9 months included foreign body giant cells, macrophages, lymphocytes, plasma cells, and a few PMN. Eosinophils were infrequently seen. To quantitate the levels of inflammation, neovascularization, and fibroblast proliferation a single pathologist who was blinded to site of

implantation graded these features using a 0-4 scale. Overall levels of inflammation and neovascularization at both sites is relatively low.

PP Mesh (n=15)	Inflammation*	Neovascularization*	Fibroblastic proliferation*
Vagina	1.5 (0.2)	1.1 (0.2)	1.5 (0.1)
Abdomen	1.2 (0.1)	0.6 (0.1)	2.0 (0.2)
p-value	.008	.02	.07

* mean (SE)

Human studies at non-genital sites

The majority of studies evaluating the host response to implanted PP mesh in humans have examined meshes used for abdominal wall hernia repairs. For example, Klosterhafen *et al.* evaluated 76 polypropylene meshes (*Marlex*) that had been removed because the hernia repairs failed, the patients had pain or developed infection.[23] It should be noted that the pore size of Marlex is half that of Prolene and about a quarter that of Prolene Soft. The median interval from implantation to mesh removal was 18 months, although one mesh was removed after 15 years. A key finding of this study was that host tissue response to PP mesh in humans is qualitatively similar to that which occurs in animal model systems. All PP mesh explants, irrespective of duration of implantation or reason for removal, had an intense scar formation. All demonstrated a chronic persistent foreign body reaction even after up to 15 years implantation. In this study a variety of immunohistochemical markers were used to identify and quantify macrophages, PMN, T-cells, B-cells, cell proliferation, and HSP 70 (heat shock protein). Additionally TUNEL in-situ histochemistry was used to identify apoptotic cells. The nature of the host tissue response to PP mesh was uniform across the patients; although the quantity and severity of the inflammatory reaction varied between patients. The amount of inflammation decreased with increasing durations of implantation, but the amount of fibrosis and blood vessels remained constant. At the interface between the mesh and host tissue, the number of macrophages and PMNs as well as proliferating cells also diminished with increasing duration of implantation. Over time the number of fibroblasts remained almost constant and an increase was seen in cells expressing HSP 70. No difference was found between PP mesh removed for pain compared to those removed for recurrence with respect to inflammatory volume, partial volume of vessels, connective tissue, inflammatory infiltrate. Meshes that were removed

because of infection showed a significant increase in the numbers of PMNs, macrophages, and lymphocytes and a reduction in fibroblasts.

Human studies at genital sites

Much of the information that we have on host tissue responses to synthetic mesh implanted in the human vagina comes from pathologic review of synthetic mesh slings of women undergoing pubovaginal sling revision. Woodruff *et al.* evaluated 24 pubovaginal slings that were explanted 2-65 months after placement.[24] 10 of these were PP mesh explants. PP mesh explants showed a greater degree of host fibroblast and tissue ingrowth than seen in either porcine dermis grafts or autologous fascia grafts. Grossly, the PP mesh lattice was completely incorporated into viable host tissue. Microscopically, host tissue ingrowth was described as abundant and occurred throughout the graft. The PP mesh explants showed the greatest degree of new blood vessel ingrowth. Despite the length of time since placement, a foreign body giant cell reaction, composed of foreign body giant cells, macrophages, and sometimes calcification, remained. None of the PP mesh explants showed evidence of degradation or encapsulation.

Recently, Hill *et al.* conducted a blinded pathological review of excised mid-urethral sling mesh from 130 subjects who presented with voiding dysfunction, pain, or exposure of the mesh (either alone or in combination). The degree of inflammation and fibrosis were graded on a 4-point scale along with the presence of a foreign body giant cell reaction.[25] Specimens from patients with voiding dysfunction only were found to be more likely to show moderate inflammation (47.6%) compared to specimens from women with pain and/or mesh exposure (26.7%) and the median grade of inflammation was higher in the voiding dysfunction group compared to the pain and/or mesh exposure group. Moderate fibrosis was seen in 61% of the specimens and there was no difference in the number having moderate fibrosis between the groups with meshes removed for different reasons. Similarly, foreign body giant cell reactions were seen in approximately 90% of all excised specimens and again did not vary based on why the mesh had been removed.

Elmer et al. conducted a study of vaginal tissue obtained from women undergoing PP mesh implants (*Prolift*) for POP.[26] In this study. 10 women undergoing pelvic surgery for POP had biopsies obtained immediately prior to the surgery. For comparison, they also obtained biopsies in 8 control women undergoing elective gynecologic surgery for other reasons. One

year after the PP mesh was implanted, a follow-up vaginal biopsy was taken close to the site of mesh insertion. Analysis of the tissues showed that a significant increase in macrophage and mast cell counts at 1 year compared to baseline but no significant change in the number of monocytes, PMN, lymphocytes, and plasma cells. Using a semi-quantitative assessment of overall inflammatory cell infiltration and vascularity, no significant change was found. Likewise, neither collagen density or elastin area fraction changed between baseline and 12 months. They concluded that PP mesh produces no adverse influence on connective tissue metabolism given the similar values for collagen density and elastin area fraction at 1 year compared to baseline.

Host Tissue Responses to *Prolene Soft* Mesh

Prolene Soft is the mesh component of *Prolift* as well as *Gynemesh PS*.[27,28] *Prolene Soft* mesh is the only component of these two devices that remains in the body. *Prolene Soft* uses the same synthetic polypropylene as Prolene that is found in Prolene suture, hernia mesh, and TVT mesh. Therefore host tissue responses to the individual fibers in *Prolene Soft* are expected to be the same seen with Prolene suture, hernia mesh, and TVT mesh. The pore size of *Prolene Soft* is larger than 1,000 um (2,500 x 1,700 um). This is large enough to allow good tissue ingrown that includes fibroblasts, macrophages, collagen, and blood vessels into the implant. The ingrowth of these connective tissue components facilitates the integration of *Prolene Soft* into the vaginal wall.[18,19,22]

The tissue studies that evaluated host tissue responses to *Prolene Soft* in both animals and humans described in the preceding sections clearly document that *Prolene Soft* evokes an initial minimal to mild acute inflammatory response, followed by a minimal to mild chronic inflammation that is accompanied by a minimal to mild fibrosis.[18,19,26] Studies that have used other forms of polypropylene mesh have shown that with longer implantation times that the host tissue response includes moderately dense fibrous connective tissue. [23,24]

Irrespective of whether one uses an animal model or evaluates human tissue, the host tissue response to *Prolene Soft* at genital locations is localized to the region of the implant.[20,21,26] The histologic studies of host response to *Prolene Soft* in either animal models or humans have not reported mesh encapsulation without integration of the mesh into the connective tissue (e.g.,

a "scar plate"). In addition, the histologic studies have not observed evidence of clinically significant degradation or disruption of the *Prolene Soft* mesh.

It is important to note that, although not specifically mentioned in either the animal or human studies of connective tissue ingrowth into PP mesh, nerves are frequently observed among the connective tissues associated with PP mesh. Innervation of the vaginal wall is predominately via the uterovaginal nerve plexus at the base of the broad ligament on either side of the supravaginal part of the cervix. The inferior fibers supply the superior part of the vagina and are derived from the inferior hypogastric plexus. These fibers are both sympathetic and parasympathetic. Anatomic studies have mapped out the distribution of nerves in the vaginal wall. These studies have higher levels of innervation on the anterior compared to the posterior wall of the vagina and also in the distal wall compared to proximal vaginal wall. [29,30]

Infection and *Prolene Soft* Mesh

Prolene Soft is classified as a Type I mesh and has a pore size of larger than 1,000 um (2,500 x 1,700 um). Type I meshes are considered to be comparatively resistant to bacterial infection compared to other types of mesh. This is because the large pore size allows PMNs and monocytes to access areas that are infected and clear the infections. Multiple studies have shown that the overall rates of infection reported for women undergoing *Prolene Soft* implants are quite low. For example, in the Scandinavian randomized trial of traditional surgery versus treatment using the *Gynecare Prolift* kit for treatment of anterior POP there were no reported cases of infection in the 200 women receiving mesh implants, 186 with 12 months follow-up.[12] Similarly, out of 524 patients with POP who were treated using *Prolift* and had 3 years of follow-up there was only one reported case of mesh infection.[31]

Conclusion

The tissue reaction to Prolene Soft mesh is an expected, non-concerning reaction. Over time, the tissue in the immediate area of the mesh shows minimal to mild chronic inflammation, foreign body reaction, and fibrosis, with incorporation into surrounding tissues. As the literature and my own experience have shown, the histologic findings cannot be correlated with clinical

complications, particularly in regards to inflammation, foreign body response, and fibrosis, where histology studies have rejected such a correlation.

Response to Images Included in General Report of Dr. Iakovlev

General comments:

The images provided by Dr. Iakovlev have a number of limitations that hinders their interpretation.

1) Many of the images are of relatively low resolution or lack focus which makes it impossible to discern the specific features that are supposedly being documented. For example, Figure set 1 supposedly shows “foreign body type inflammatory reaction”, yet except for a few giant cells, it is impossible to discern what types of cells are present in the inflammatory infiltrate.

2) Some of the images appear to be labeled with the incorrect magnification. For example, Figure 2c is listed as being 4x, whereas Figure 2d is listed as being 1.6x. However 2d is at a higher magnification than 2c.

3) Immunohistochemical stains are presented without accompanying H&E stained sections to allow correlation between what is seen in the immunohistochemical stained section with the accompanying histological features. Appropriate controls for the immunohistochemical stains are neither mentioned nor presented. Some of the immunohistochemical stains appear to have high background staining (Figure 2g).

Specific Comments:

Figure set 1 is presented as representative of the foreign body response to the Ethicon transvaginal mesh. The images shown in Figure 1a are not representative. Instead, they represent areas with a prominent response. Many implanted mesh fibers will show a minimal inflammatory response as can be seen in Figure 2c. It should also be noted that even in these areas with a prominent response, the inflammatory infiltrate is actually relatively mild and is localized to the region immediately adjacent to the mesh. A short distance away from the mesh fibers, there is loose fibrous connective tissue with minimal inflammation present.

Figure set 2 is presented as showing a scar plate formation. These photos are labeled fibrous bridging and scar encapsulation. What they actually show is the expected fibrous connective tissue ingrowth into the implanted mesh. This is the desired host response to the implanted mesh and is the biological response that results in repair of a pelvic organ prolapse patient's vaginal wall defect. The photographs do not show "scar encapsulation". Encapsulation is used pathologically to refer to a process where there is a fibrous capsule that forms around a structure. Since the fibrous connective tissue in these photographs has integrated into the mesh, it is incorrect to refer to it as "encapsulating the mesh". Figure 2g shows how limited the fibrous connective tissue response is to the implanted mesh since smooth muscle fibers (bottom) and adipose tissue (top) are quite close to the actual fibers. Many of the interpretations of the photographs are highly subjective and would not be considered acceptable in a scientific presentation or paper. For example, in Figure 2e it is stated that there is "normal non scarred adipose tissue (fat) outside of the mesh-scar plate". In addition to fibrous connective tissue, adipose tissue can infiltrate into large pore meshes and at the top of the figure you can also see adipose tissue that is located between mesh fibers. This is also shown in Figure 2g. Therefore there is no data to support the contention that the area of adipose tissue labeled "Fat" is actually "normal non scarred adipose tissue". Figure 2g shows a low magnification view of mesh and accompanying fibrous connective tissue. The immunohistochemically stained photograph in 2g appears to be from a different implant or a different region of the tissue than the figure above it. Finding smooth muscle adjacent to mesh fibers has no pathological significance. There are many sources of smooth muscle in the pelvis and it is impossible to know if the smooth muscle shown in 2g is from the vaginal wall. During vaginal mesh implantation it is not unexpected that mesh would be placed in proximity to smooth muscle.

Figure sets 3 and 4 show small nerve branches and ganglia in the fibrous connective tissue that has grown into the mesh pores. These photographs are reported to document damage to nerves and vessels by the mesh. When small nerve branches are severed (as they inevitably are during surgery) the nerves will attempt to regenerate and form many small nerve twigs. Therefore one would expect to find small nerve branches and even ganglion in the fibrous connective tissue formed in response to the implantation of mesh. Showing that some of these nerves appear to be "distorted" by the mesh in histological sections is meaningless since it is impossible to know whether the apparent "distortion" was present prior to removal, or occurred during removal of the mesh, or during fixation and histological processing. Without the use of

special stains to document nerve damage, it is impossible to tell whether or not the nerve is damaged in either H&E or S100 stained sections. It is incorrect to correlate the appearance of these nerves on H&E stained slides with the clinical symptom of pelvic pain. Not only is it unclear that the nerves are damaged (see above), but in the absence of functional studies, we do not know if the nerves are even capable of transmitting pain or if there are receptors in the tissue. Nerves which are labeled as being severely distorted by mesh appear histologically normal (Figure 3c).

Figure set 5 shows normal vaginal mucosa overlying mesh with a normal degree of innervation. The section is stained with S100 and shows what may be a number of small nerves in the lamina propria. The majority of the vaginal innervation is autonomic and it is impossible without functional studies to determine the type of nerves that these represent.

Figure set 6 shows mesh together with associated fibrous connective tissue. Although the Figure set is labeled “Vascular dilatation and tissue edema,” the photomicrographs show simply the normal blood vessels that are seen associated with fibrous connective tissue. All of the vessels are of a normal caliber. With respect to edema, I see no histological evidence of edema. I see areas of both loose fibrous connective tissue and denser fibrous connective tissue. Moreover, during explant surgery manipulation of the mesh and hydrodissection can cause histological artifacts in fibrous connective tissue. The magnification in Figure 6d is too low to make out the structures labeled “fluid bubbles (edema)”

Figure set 7 is supposed to show involvement of striated muscle. Many of the photographs are too low magnification to be interpreted. It should be stressed that there are a number of structures composed of striated muscle that are involved in pelvic reconstructive surgery. Therefore, the presence of mesh adjacent to striated muscle as is seen in Figure 7a (if in fact this is striated muscle) is expected. Although the photograph is very low magnification, there appears to be no associated inflammation in what is labeled “Striated muscle”. In Figure 7b, it is impossible to tell what the “Scarred muscle” consists of. To conclude that the muscle is scarred, a Trichrome stain should be provided. In Figure 7c, degenerated striated muscle is frequently seen at the site of previous surgery and there is no inflammation present. There also are no adjacent mesh fibers.

Figure set 8 is supposed to show the appearance of mesh adjacent to pelvic structures such as the bladder, rectum, and urethra. The female pelvis contains many different structures that contain smooth muscle including the vaginal wall, the rectovaginal septum, many of the fascia,

and the major ligaments, as well as the bladder, rectum, and urethra. Explanted mesh fragments are often removed in multiple pieces including pieces from the anterior and posterior vaginal walls and are typically submitted to pathology unoriented in a single container. Unless the surgeon has specifically labeled a fragment with respect to its orientation in the body, it is pure speculation to attribute smooth muscle seen on the histology specimen with a specific anatomical site.

Figure set 9 demonstrates arterial obliteration. Arterial obliteration is common finding in gynecological surgical specimens from post-menopausal women, especially those with a history of prior surgery. This finding has no clinical significance since there is no functional correlate.

Figure sets 10 and 11 purportedly show folding of mesh within the body. When explanted from the body the mesh and associated fibrous connective tissue can fold and will be fixed into the folded shape that did not exist in the body. Moreover, during surgery and histological processing the mesh and tissue will be subject to a variety of stresses. Ethicon *Prolift* and *Gynemesh PS* are pliable 3-dimensional structures and as explained in my discussion of Figure set 8, it is almost impossible to determine how the mesh was oriented in vivo once it has been sectioned. The yellow colored lines that Dr. Iakovlev has drawn in on Figure sets 10 and 11 are completely arbitrary and I could easily draw others that could also correlate to the known 3-dimensional structure of *Prolift* and *Gynemesh PS.*

Figure set 12 is supposed to show mesh erosion though the vaginal mucosa. There is no question that vaginal mesh exposures occur. If mesh becomes exposed, histological sections of mesh from this area will show mesh fibers present in a region with acute inflammation, granulation tissue, and sometimes bacteria. However, ulcerations of the vaginal epithelium unassociated with implanted mesh are common in postmenopausal women. This is usually associated with atrophy of the vaginal mucosa and the vaginal wall and sometimes coexisting infection. When ulcerations occur they can become infected and show granulation tissue together with bacteria.

Figure set 13-19 these photographs are supposed to document that polypropylene degrades in the body and that this degradation impacts the performance of the mesh. What the photographs actually document is the presence of a thin rim of birefringent material that stains blue-grey with H&E stains. At high magnification, small cracks can be seen in this material that Dr. Iakovlev refers to as “degradation bark”. The bulk of the polypropylene filament that is surrounded by this thin layer is intact. Although the exact composition of this thin rim of

birefringent material is unknown, it's stain characteristics suggest that it contains an admixture of polypropylene (hence it's birefringence) as well as protein (since it stains with H&E stain whereas polypropylene does not). During processing for histology, tissue (including the polypropylene mesh) is initially fixed in formalin which cross-links proteins and is then dehydrated though an increasing series of ethanol concentrations and the ethanol is then cleared by incubation in multiple xylene baths. This is followed by infiltration with histological wax in liquid form at 60o C. Polypropylene is not resistant to xylene.[32] A proteinaceous layer rapidly forms on biocompatible foreign materials when implanted in tissue and this proteinaceous layer would become cross-linked during routine formalin fixation.[15,33] Dr. Iakovlev has presented no scientifically valid evidence to demonstrate the nature of this material and when it was formed.

Even if Dr. Iakovlev's hypothesis that this material represents degraded polypropylene and was actually present in the body prior to processing is correct, there is no scientifically valid indication that this thin rim of material impacts the structural integrity of the polypropylene fiber. Indeed, identical layers of birefringent material are frequently seen on polypropylene sutures that are utilized for other types of surgery.

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FEE Schedule

$400.00 per hour for case review, preparation, deposition, and trial testimony

Depositions and trials within the last 4 years

Susan Starrett v Noman Siddiqui, MD

Deposition Dates	July 22, 2014
	February 10, 2015
Trial	November 18, 2015